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14461 U.S. PTO
08/12/03

Docket No.: 58883US002

Transmittal of Provisional Application

Mail Stop Provisional Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Inventor(s): Tushar Kshirsagar, Woodbury, Minnesota

Title: OXIME SUBSTITUTED IMIDAZOQUINOLINES

16235 U.S. PTO
60/494608
08/12/03

1. ☒ Enclosed is the above-identical new provisional application for patent under 35 USC § 111(b)(1). It includes:
   66 Pages of Text
   0 Sheets of Drawings
2. ☐ Enclosed is an executed Assignment to 3M Innovative Properties Company and a completed Assignment Recordation Cover Sheet.
3. ☐ This invention was made under a contract with an agency of the U.S. Government:
   Agency: ___________
   Contract No. ___________
4. ☒ Correspondence Address: Dean A. Ersfeld
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   P.O. Box 33427
   St. Paul, Minnesota 55133-3427
5. ☒ Please charge the $160.00 filing fee under 37 CFR § 1.16(k) to Deposit Account No. 13-3723. One copy of this sheet marked duplicate is also enclosed.
6. ☒ Please charge to Deposit Account No. 13-3723 any fees under 37 CFR §§ 1.16 and 1.17, which may be required to file and during the entire pendency of this application. This authorization includes the fee for any necessary extension of time under 37 CFR § 1.136(a). To the extent any such extension should become necessary, it is hereby requested.
7. ☒ Enclosed is a return receipt postcard.

Respectfully submitted,

12 August 2003
Date

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Filing of Papers and Fees by Express Mailing

Pursuant to 37 CFR § 1.10, this application and the documents and fees listed on this transmittal letter are being deposited on the date indicated below with the United States Postal Service "Express Mail Post Office to Addressee" service addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

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OXIME SUBSTITUTED IMIDAZOQUINOLINES

BACKGROUND

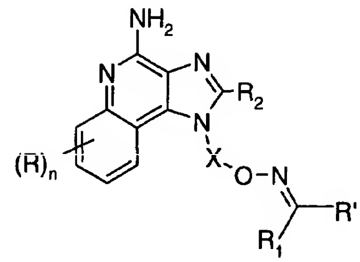
In the 1950's the 1*H*-imidazo[4,5-*c*]quinoline ring system was developed, and 1-(6-methoxy-8-quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline was synthesized for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*] quinolines were reported. For example, 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline was synthesized as a possible anticonvulsant and cardiovascular agent. Also, several 2-oxoimidazo[4,5-*c*]quinolines have been reported.

Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators.

There continues to be interest in the imidazoquinoline ring system and there is a continuing need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

SUMMARY

The present invention provides a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Such compounds are of the following Formula (I):



I

wherein: X, R, R', n, R_1, and R_2 are as defined below.

The compounds of Formula I are useful as immune response modifiers due to their ability to induce cytokine biosynthesis (e.g., induces the synthesis of at least one cytokine) and otherwise modulate the immune response when administered to animals. This makes the compounds useful in the treatment of a variety of conditions such as viral diseases and tumors that are responsive to such changes in the immune response.

The invention further provides pharmaceutical compositions containing an effective amount of a compound of Formula I and methods of inducing cytokine biosynthesis in an animal, treating a viral infection and/or treating a neoplastic disease in an animal by administering an effective amount of a compound of Formula I to the animal.

In addition, methods of synthesizing compounds of Formula I and intermediates useful in the synthesis of these compounds are provided.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

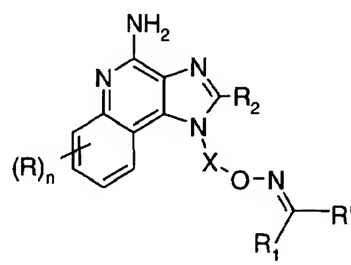
The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the description, guidance is provided through lists of

examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

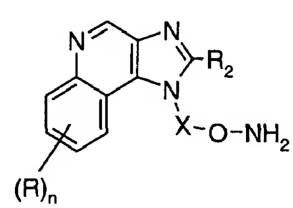
DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides compounds of the following Formula (I):

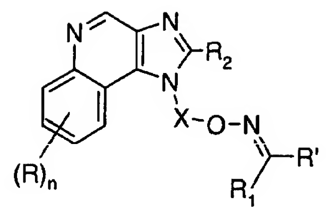


I

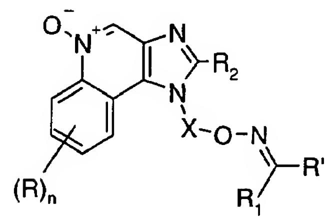
as well as intermediates of the following Formulas (XIV, XV, XVI):



XIV



XV



XVI

wherein:

X is –CH(R_4)alkylene or –CH(R_4)alkenylene;

R_1 and R' are independently selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-alkylene-aryl;

-heteroaryl;

-heterocyclyl; and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl or heterocyclyl substituted by one or more substituents selected from the group consisting of:

-OH;

-alkyl;

-haloalkyl;

-hydroxyalkyl;

-O-alkyl;

-S-alkyl;

-O-haloalkyl;

-halogen;

-nitrile;

-aryl;

-heteroaryl;

-heterocyclyl;

-O-aryl;

-O-alkylene-aryl;

-C(O)-O-alkyl;

-C(O)-N(R_5)$_2$; and

-N(R_5)-C(O)-alkyl;

or R_1 and R' can join together to form a ring system containing one or two saturated or unsaturated rings optionally including one or more heteroatoms;

n is 0-4;

each R and R_2 are independently selected from the group consisting of hydrogen and non-interfering substituents;

R_4 is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups; and

each R_5 is independently selected from the group consisting of hydrogen, C_{1-10}alkyl, and C_{2-10}alkenyl;

or a pharmaceutically acceptable salt thereof.

Herein, "non-interfering" means that the immunomodulator activity of the compound is not destroyed.

For certain embodiments of Formulas I, XV, and XVI, R_1 and R' join together to form a ring system. The ring system is optionally substituted by one or more substituents selected from the group consisting of -alkyl, -aryl, -alkylene-aryl, and -C(O)-alkyl. Also, one of skill in the art would understand that the ring system

would not include an aromatic ring attached to the N=C moiety. Furthermore, the size and components of the ring system are not limiting as long as they do not destroy the immunomodulator activity of the compound (i.e., they are non-interfering). Typically, this means that the ring system is a monocyclic ring system containing 5 to 8 atoms in the ring or a bicyclic ring system containing 9 to 11 atoms in the ring. For certain embodiments of Formulas I, XV, and XVI, the ring system contains one or two heteratoms (e.g., O, S, N). For certain embodiments of Formulas I, XV, and XVI, R_1 and R' join to form a ring system selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, piperidinyl, and indanyl.

For certain embodiments of Formulas I, XIV, XV, and XVI, X is $CH(R_4)C_{1-5}$alkylene and for other embodiments X is propylene or butylene.

For certain embodiments of Formulas I, XV, and XVI, R_1 is selected from the group consisting of -aryl, -heteroaryl, and -alkyl, wherein the -aryl, -heteroaryl, and -alkyl are optionally substituted. For certain other embodiments R_1 is aryl or substituted aryl. For certain other embodiments, R_1 is heteroaryl or substituted heteroaryl.

For certain embodiments of Formulas I, XIV, XV, and XVI, n is 0.

For certain embodiments of Formulas I, XV, and XVI, R' is hydrogen.

For certain embodiments of Formulas I, XIV, XV, and XVI, each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl.

For certain embodiments of Formulas I, XIV, XV, and XVI, R_2 is selected from the group consisting of:

- -hydrogen;
- -alkyl;
- -alkenyl;
- -aryl;
- -heteroaryl;
- -heterocyclyl;
- -alkylene-Y-alkyl;

-alkylene-Y- alkenyl;

-alkylene-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_5)_2$;

-C(O)-C_{1-10}alkyl;

-C(O)-O-C_{1-10}alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-C(O)-aryl; and

-C(O)-heteroaryl;

wherein:

Y is –O– or –$S(O)_{0-2}$-; and

each R_5 is independently selected from the group consisting of hydrogen, C_{1-10}alkyl, and C_{2-10}alkenyl.

For certain other embodiments of Formulas I, XIV, XV, and XVI, R_2 is selected from the group consisting of hydrogen, alkyl, and alkylene-O-alkyl.

As used herein, the terms "alkyl," "alkenyl," "alkynyl," and the prefix "alk-" are inclusive of both straight chain and branched chain groups and, in the case of alkyl and alkenyl, of cyclic groups, i.e., cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl and alkynyl groups containing from 2 to 20 carbon atoms. The alkenyl and alkynyl groups can contain one or more double and triple bonds respectively. In some embodiments, preferred groups have a total of up to 10 carbon atoms. In other embodiments, preferred groups have a total of up to 8, up to 6, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3

to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, adamantyl, norbornane, and norbornene.

The terms "alkylene," "alkenylene," and "alkynylene" are inclusive of divalent radicals derived from the alkyl, alkenyl, and alkynyl groups described above.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of groups that include the prefix "halo-." Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl. The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, and so on.

The terms "arylene" and "heteroarylene" include divalent radicals derived from the aryl and heteroaryl groups described above.

"Heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, isothiazolidinyl, and imidazolidinyl.

The term "heterocyclylene" includes divalent radicals derived from the heterocyclyl groups described above.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and

enantiomers, salts, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers.

Preparation of the Compounds

Compounds of the invention can be prepared according to Route 1 of Reaction Scheme I where R_1, R_2, R, R', X, and n are as defined above. In step (1) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinolin-1-yl alcohol of Formula X is treated with *N*-hydroxyphthalimide under Mitsunobu reaction conditions to provide an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-1-yl hydroxylamine of Formula XI. The reaction is conveniently carried out by adding triphenylphosphine and *N*-hydroxyphthalimide to a solution of the alcohol of Formula X in a suitable solvent such as tetrahydrofuran and then slowly adding diisopropyl azodicarboxylate. The reaction can be carried out at ambient temperature or at an elevated temperature, such as 60°C. The product can be isolated using conventional methods. Many compounds of Formula X are known; see for example, U.S. Patent 4,689,338 (Gerster). Others can be readily prepared using known synthetic routes; see for example, U.S. Patent 5,605,899 (Gerster et al.) and U.S. Patent 5,175,296 (Gerster).

In step (2) of Reaction Scheme I, an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-1-yl hydroxylamine of Formula XI is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XII using a conventional oxidizing agent capable of forming *N*-oxides. The reaction is conveniently carried out by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XI in a solvent such as chloroform or dichloromethane. The reaction can be carried out at ambient temperature. The product can be isolated using conventional methods.

In step (3) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XII is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XIII. Step (3) involves the activation of an *N*-oxide of Formula XII by

conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction is conveniently carried out by adding ammonium hydroxide to a solution of the *N*-oxide of Formula XII in a suitable solvent such as dichloromethane or chloroform and then adding *p*-toluenesulfonyl chloride. The reaction can be carried out at ambient temperature. Under these reaction conditions, the *N*-phthalimide protecting group is removed to provide the 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XIII, which can be isolated from the reaction mixture using conventional methods.

In step (4) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XIII reacts with an aldehyde or ketone of Formula $R_1C(O)R'$ to provide a 1*H*-imidazo[4,5-*c*]quinolin-1-yl oxime of Formula I. Numerous aldehydes and ketones of Formula $R_1C(O)R'$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the aldehyde or ketone of Formula $R_1C(O)R'$ to a solution of the 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XIII in a suitable solvent such as methanol. The reaction can be carried out at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Compounds of the invention can be prepared by an alternative route shown as Route 2 in Reaction Scheme I where R_1, R_2, R, R', X, and n are as defined above. In step (1a) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinolin-1-yl alcohol of Formula X is converted to a 1*H*-imidazo[4,5-*c*]quinolin-1-yl hydroxylamine of Formula XIV. The reaction is carried out under Mitsunobu reaction conditions as described for step (1) of Route 1, and during the isolation of the reaction product, the *N*-phthalimide protecting group is removed by treatment with a strong base. Conveniently, an acidic aqueous solution of an *N*-phthalimide-protected 1*H*-

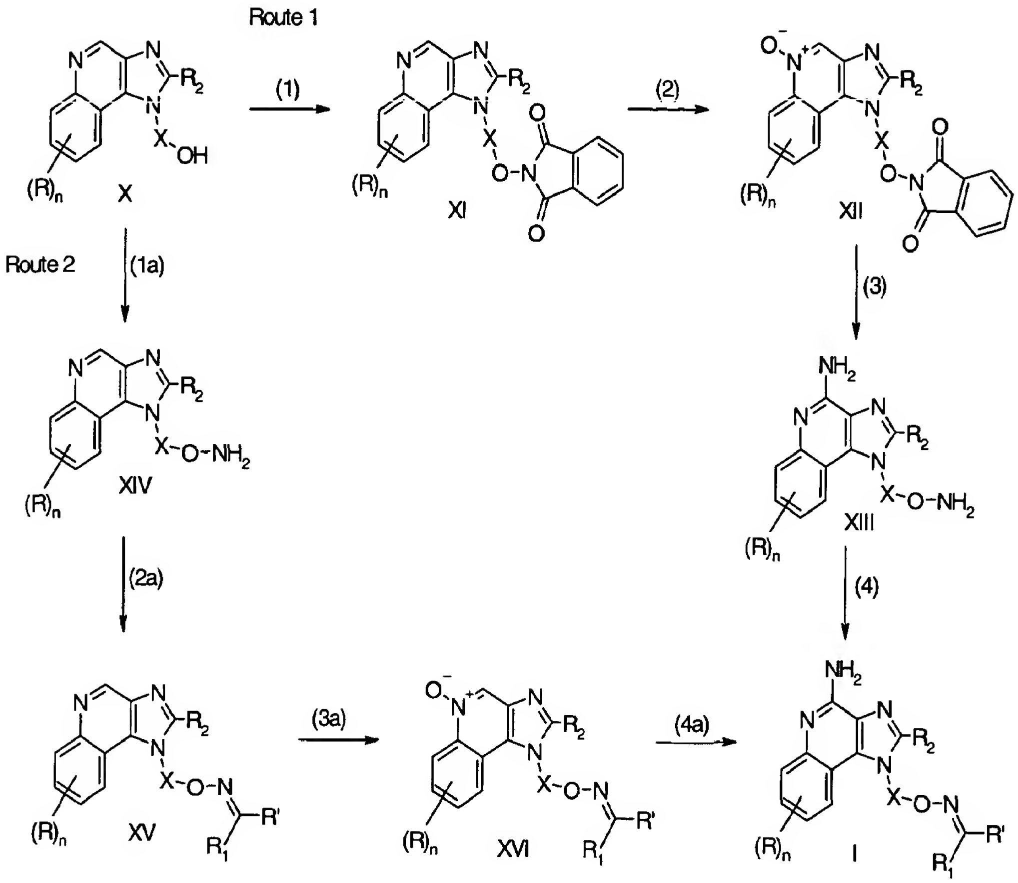
imidazo[4,5-*c*]quinolin-1-yl hydroxylamine of Formula XI is treated with sodium hydroxide until the pH of the solution is basic. The 1*H*-imidazo[4,5-*c*]quinolin-1-yl hydroxylamine of Formula XIV can then be isolated using conventional methods. Many compounds of Formula X are known or can be prepared using known synthetic methods as described above in step (1) of Route 1.

In step (2a) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinolin-1-yl hydroxylamine of Formula XIV reacts with an aldehyde or ketone of Formula $R_1C(O)R'$ to provide a 1*H*-imidazo[4,5-*c*]quinolin-1-yl oxime of Formula XV. Numerous aldehydes and ketones of Formula $R_1C(O)R'$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be carried out as described above in step (4) of Route 1.

In step (3a) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinolin-1-yl oxime of Formula XV is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XVI using a conventional oxidizing agent capable of forming *N*-oxides. The reaction can be carried out as described above in step (2) of Route 1.

In step (4a) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XVI is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula I. The reaction can be carried out as described above in step (3) of Route 1. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme I



Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain an effective amount of a compound of the invention as described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "an effective amount" mean an amount of the compound sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the

compound, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

The compounds of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds are useful as immune response modifiers (IRMs) that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds according to the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or composition of the invention to the animal. The animal to which the compound or composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral

disease or a neoplastic disease, or the animal may not have a disease, but instead be given the compound or composition for prophylaxis of a disease, for example a viral disease or a neoplastic disease. For prophylaxis of a disease, the compound or composition may be administered, for example, as a vaccine adjuvant. Thus, treatment may be therapeutic and/or prophylactic.

In addition to the ability to induce the production of cytokines, the compounds of the invention affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds may cause proliferation and differentiation of B-lymphocytes.

Compounds of the invention also have an effect on the acquired immune response. For example, the production of the T helper type 1 (Th1) cytokine IFN-γ is induced indirectly and the production of the T helper type 2 (Th2) cytokines IL-4, IL-5 and IL-13 are inhibited upon administration of the compounds.

Diseases for which IRMs identified herein may be used as treatments include, but are not limited to:

(a) viral diseases, such as genital warts, common warts, plantar warts, hepatitis B, hepatitis C, herpes simplex virus type I and type II, molluscum contagiosum, variola, HIV, CMV, VZV, rhinovirus, adenovirus, coronavirus, influenza, and para-influenza;

(b) bacterial diseases, such as tuberculosis, mycobacterium avium, and leprosy;

(c) other infectious diseases, such as fungal diseases, chlamydia, candida, aspergillus, cryptococcal meningitis, pneumocystis carnii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection, and leishmaniasis;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, hairy cell leukemia, Karposi's sarcoma, melanoma, renal cell carcinoma, myelogeous

leukemia, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, and other cancers;

(e) Th2 mediated, atopic, and autoimmune diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, systemic lupus erythematosis, essential thrombocythaemia, multiple sclerosis, Ommen's syndrome, discoid lupus, alopecia areata, inhibition of keloid formation and other types of scarring, and enhancing would healing, including chronic wounds; and

(f) as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such live viral and bacterial immunogens and inactivated viral, tumor-derived, protozoal, organism-derived, fungal, and bacterial immunogens, toxoids, toxins, polysaccharides, proteins, glycoproteins, peptides, cellular vaccines, DNA vaccines, recombinant proteins, glycoproteins, and peptides, and the like, for use in connection with, e.g., BCG, cholera, plague, typhoid, hepatitis A, B, and C, influenza A and B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, and yellow fever.

IRMs may also be particularly helpful in individuals having compromised immune function. For example, IRM compounds may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need there of (having the disease) by administering an effective amount of a compound or salt of formula (I) to the animal.

An amount of a compound effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages,

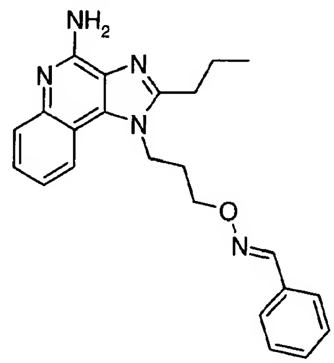
dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10, and IL-12 that is increased over the background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg.

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

Example 1

Benzaldehyde *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime



Part A

A solution of 1-(3-hydroxypropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinoline (20.0 grams (g), 74.3 millimoles (mmol)) in tetrahydrofuran (300 milliliters (mL)) was cooled to approximately 0°C; triphenylphosphine (23.4 g, 89.1 mmol) and *N*-hydroxyphthalimide (14.5 g, 89.1 mmol) were then added. After five minutes of stirring, diisopropyl azodicarboxylate (17.5 mL, 89.1 mmol) was added dropwise over a period of 15 minutes (min). The reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure, and the residue was dissolved in chloroform (300 mL). A solution of hydrochloric acid (150 mL of 6 molar (M)) was then added, and approximately 50 mL of the solvent was removed under reduced pressure to provide a white precipitate, which was stirred for ten minutes and isolated by filtration. Additional salt eventually precipitated from the filtrate and was isolated by filtration. Chloroform (300 mL) and water (300 mL) were added to the salt, and solid sodium bicarbonate was added to the mixture to adjust to pH 8. The organic solution was then dried over magnesium sulfate, filtered, and concentrated under reduced

pressure to provide 28.4 g of 2-[3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propoxy]isoindole-1,3-dione as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.3 (s, 1H), 8.3 (m, 2H), 7.9 (m, 2H), 7.8 (m, 2H), 7.6 (m, 2H), 5.0 (t, *J* = 7.3 Hz, 2H), 4.4 (t, *J* = 5.3 Hz, 2H), 3.1 (t, *J* = 7.5 Hz, 2H), 2.4 (m, 2H), 2.1 (br s, m, 4H), 1.2 (t, *J* = 7.3 Hz, 3H);

MS (APCI) *m/z* 415 $(M + H)^+$.

Part B

3-Chloroperoxybenzoic acid (14.9 g, 66.4 mmol) (mCPBA, available as an approximately 77% pure mixture) was added to a solution of 2-[3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propoxy]isoindole-1,3-dione (25.0 g, 60.3 mmol) in chloroform (200 mL), and the reaction was stirred for seven hours at room temperature. An analysis by liquid chromatography/mass spectrometry (LC/MS) indicated that the reaction was incomplete, and additional mCPBA (4.96 g, 22.1 mmol) was added. The reaction was allowed to stir at room temperature overnight. The solution was then washed with brine (2 x 100 mL) and saturated aqueous sodium bicarbonate (2 x 100 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide a fluffy, light-brown solid. The solid was dried under high vacuum for one hour to provide 25.7 g of 2-[3-(5-oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propoxy]isoindole-1,3-dione as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.1 (m, 2H), 8.3 (m, 1H), 7.9-7.7 (m, 6H), 5.0 (t, *J* = 7.4 Hz, 2H), 4.4 (t, *J* = 5.3 Hz, 2H), 3.1 (t, *J* = 7.5 Hz, 2H), 2.4 (m, 2H), 2.1 (br s, m, 4H), 1.2 (t, *J* = 7.3 Hz, 3H);

MS (APCI) *m/z* 431 $(M + H)^+$.

Part C

Ammonium hydroxide (75 mL) and *p*-toluenesulfonyl chloride (4.87 g, 25.6 mmol) were added to a solution of 2-[3-(5-oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propoxy]isoindole-1,3-dione (10.0 g, 23.2 mmol) in chloroform

(100 mL), and the resulting mixture was stirred vigorously for one hour. A white precipitate was removed by filtration, and the filtrate layers were separated. The organic solution was washed with brine (2 x 150 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide a yellow solid. The solid was purified by column chromatography on silica gel (eluting with dichloromethane:methanol:ammonium hydroxide ranging in ratios from 94:5:1 to 91:8:1) to provide 4.31 g of *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]hydroxylamine as a beige powder, melting point (mp) 145-148°C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.1 (d, *J* = 7.5 Hz, 1H), 7.6 (d, *J* = 8.3 Hz, 1H), 7.4 (t, *J* = 8.1 Hz, 1H), 7.3 (t, *J* = 8.1 Hz, 1H), 6.5 (br s, 2H), 6.1 (br s, 2H), 4.6 (t, *J* = 7.2 Hz, 2H), 3.6 (t, *J* = 5.6 Hz, 2H), 2.9 (t, *J* = 7.4 Hz, 2H), 2.1 (m, 2H), 1.9 (m, 2H), 1.1 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (75 MHz, DMSO-d_6) δ 153.4, 152.0, 145.0, 132.6, 126.8, 126.6, 121.5, 120.4, 115.1, 71.6, 42.5, 29.2, 28.5, 21.3, 14.2;

MS (APCI) *m/z* 300 $(M + H)^+$;

Anal. calcd for $C_{16}H_{21}N_5O$: C, 64.19; H, 7.07; N, 23.39. Found: C, 63.94; H, 7.20; N, 23.11.

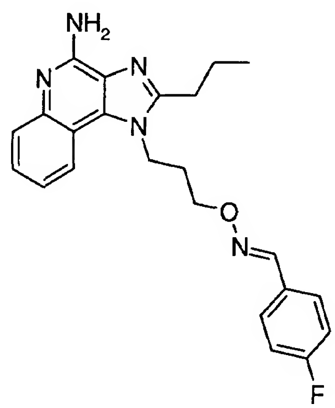
Part D

Benzaldehyde (383 µL, 3.77 mmol) was added to a mixture of *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]hydroxylamine (0.800 g, 2.68 mmol) in methanol (15 mL), and the resulting red solution was stirred for two hours. The reaction was then concentrated under reduced pressure, and the residue was purified twice by column chromatography on silica gel (50-60 g, eluting sequentially with 98:2 dichloromethane:methanol and 95:5 dichloromethane:methanol) to provide 0.580 g of benzaldehyde *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime as a beige powder, mp 125-128 °C.

^{1}H NMR (300 MHz, $CDCl_3$) 8.1 (s, 1H), 8.0 (d, J = 7.5 Hz, 1H), 7.8 (d, J = 8.3 Hz, 1H), 7.6 (m, 2H), 7.5 (m, 4H), 7.2 (m, 1H), 5.6 (br s, 2H), 4.6 (t, J = 7.5 Hz, 2H), 4.3 (t, J = 5.5 Hz, 2H), 2.9 (t, J = 7.6 Hz, 2H), 2.4 (m, 2H), 1.9 (m, 2H), 1.1 (t, J = 7.4 Hz, 3H);
^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 151.2, 149.4, 144.6, 133.2, 131.9, 130.8, 130.2, 128.2, 127.1, 126.9, 122.2, 119.6, 115.4, 70.5, 42.7, 30.0, 29.2, 21.5, 14.0;
MS (APCI) m/z 388 $(M + H)^+$;
Anal. calcd for $C_{23}H_{25}N_5O \bullet 0.37H_2O$: C, 70.09; H, 6.58; N, 17.77. Found: C, 69.75; H, 6.60; N, 17.49.

Example 2

4-Fluorobenzaldehyde *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime



4-Fluorobenzaldehyde (307 µL, 2.86 mmol) was added to a mixture of *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]hydroxylamine (0.800 g, 2.68 mmol) in methanol (15 mL), and the resulting red solution was stirred for two hours. The reaction was then concentrated under reduced pressure, and the residue was purified twice by column chromatography on silica gel (50-60 g, eluting sequentially with 98:2 dichloromethane:methanol and 95:5 dichloromethane:methanol) to provide 600 mg of 4-fluorobenzaldehyde *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime as a beige powder, mp 172-175°C.

^1H NMR (300 MHz, $CDCl_3$) δ 8.1 (s, 1H), 8.0 (d, J = 8.2 Hz, 1H), 7.8 (d, J = 7.8 Hz, 1H), 7.6 (m, 2H), 7.56 (m, 1H), 7.4 (m, 1H), 7.1 (m, 2H), 5.6 (br s, 2H), 4.6 (t, J = 7.5 Hz, 2H), 4.3 (t, J = 5.5 Hz, 2H), 2.9 (t, J = 7.6 Hz, 2H), 2.4 (m, 2H), 1.9 (m, 2H), 1.1 (t, J = 7.3 Hz, 3H);

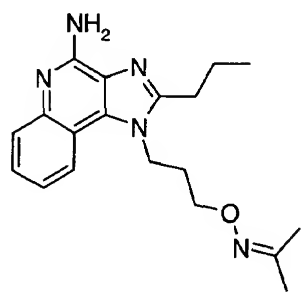
^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9,162.6, 153.7, 151.6, 148.5, 145.7, 145.0, 133.6, 129.4, 129.3, 128.5, 127.5, 127.3, 122.6, 120.0, 116.5, 116.2, 115.8, 70.9, 43.1, 30.3, 29.6, 21.9, 14.4;

MS (APCI) m/z 406 $(M + H)^+$;

Anal. calcd for $C_{23}H_{24}FN_5O$: C, 68.13; H, 5.97; N, 17.27. Found: C, 67.82; H, 6.14; N, 16.94.

Example 3

Propan-2-one *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime



A mixture of *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]hydroxylamine (0.605 g, 2.02 mmol) in methanol was heated until the starting material dissolved. Acetone (3 mL, 40 mmol) was then added, and the resulting solution was stirred for two hours. The reaction was then concentrated under reduced pressure, and the residue (800 mg) was purified by column chromatography on silica gel (25 g, eluting sequentially with 98:2 dichloromethane:methanol and 95:5 dichloromethane:methanol) to provide 600 mg of propan-2-one *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime as a beige powder, mp 147-150°C.

^1H NMR (300 MHz, $CDCl_3$) δ 8.0 (d, J = 8.2 Hz, 1H), 7.8 (d, J = 8.4 Hz, 1H), 7.5 (t, J = 7.1 Hz, 1H), 7.3 (t, J = 8.4 Hz, 1H), 5.6 (br s, 2H), 4.6 (t, J = 7.6 Hz, 2H), 4.2 (t, J = 5.5 Hz, 2H), 2.9 (t, J = 7.6 Hz, 2H), 2.3 (m, 2H), 2.0 (m, 8H), 1.1 (t, J = 7.3 Hz, 3H);

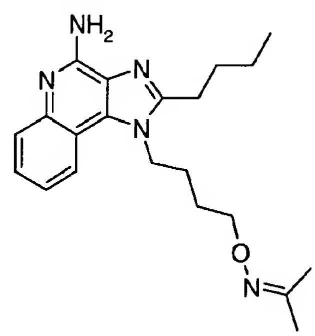
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 153.3, 151.2, 144.7, 133.2, 127.1, 126.9, 122.1, 119.7, 115.5, 69.5, 42.9, 30.0, 29.2, 21.9, 21.6, 15.6, 14.1;

MS (APCI) m/z 340 $(M + H)^+$;

Anal. Calcd for $C_{19}H_{25}N_5O \bullet 0.35H_2O$: C, 66.00; H, 7.49; N, 20.26. Found: C, 66.34; H, 7.34; N, 19.88.

Example 4

Propan-2-one *O*-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]oxime



Part A

Triphenylphosphine (21.2 g, 80.7 mmol) and *N*-hydroxyphthalimide (13.2 g, 80.7 mmol) were added to a solution of 2-butyl-1-(4-hydroxybutyl)-1*H*-imidazo[4,5-*c*]quinoline (16.0 g, 53.8 mmol) in tetrahydrofuran (200 mL). The mixture was stirred for five minutes and then was cooled to approximately 0 °C. Diisopropyl azodicarboxylate (19.6 g, 96.8 mmol) was added dropwise, and the reaction was allowed to warm to room temperature and stirred for three hours. An analysis by LC/MS indicated the presence of starting material, and the reaction was stirred at 60 °C overnight. An analysis by LC/MS indicated the presence of starting material, and additional triphenylphosphine, *N*-hydroxyphthalimide, and diisopropyl azodicarboxylate (26.9 mmol of each) were added to the reaction mixture. The

reaction was stirred at room temperature for two hours and heated at reflux for three hours. The reaction was concentrated under reduced pressure, and the residue was dissolved in chloroform (200 mL). The resulting solution was washed with brine (3 x 150 mL), dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and concentrated under reduced pressure. An analysis of the crude product mixture by LC/MS indicated that starting material was still present. The mixture was dissolved in tetrahydrofuran (200 mL) and treated with triphenylphosphine (21.2 g, 80.7 mmol), *N*-hydroxyphthalimide (13.2 g, 80.7 mmol), and diisopropyl azodicarboxylate (19.6 g, 96.8 mmol) as described above. The reaction was stirred overnight at room temperature. The product was present as a white precipitate, which was isolated by filtration and washed with tetrahydrofuran to provide 8.68 g of 2-[4-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]isoindole-1,3-dione as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.3 (s, 1H), 8.3 (m, 2H), 7.9 (m, 2H), 7.8 (m, 2H), 7.7 (m, 2H), 4.7 (t, J = 7.9 Hz, 2H), 4.3 (t, J = 5.8 Hz, 2H), 3.1 (t, J = 7.6 Hz, 2H), 2.3 (m, 2H), 2.0 (m, 4H), 1.6 (m, 2H), 1.1 (t, J = 7.3 Hz, 3H);
MS (APCI) *m/z* 443 $(M + H)^+$.

Part B

A solution of 2-[4-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]isoindole-1,3-dione (7.65 g, 17.3 mmol) in dichloromethane (100 mL) was treated with mCPBA (4.65 g, 20.7 mmol), and the resulting orange solution was stirred for four hours at room temperature. The solution was then diluted with dichloromethane (100 ml), washed with brine (3 x 100 mL), dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and concentrated under reduced pressure to provide 9.92 g of 2-[4-(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]isoindole-1,3-dione as a red semi-solid.

Part C

A mixture of 2-[4-(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]isoindole-1,3-dione (8.92 g, 19.5 mmol) in dichloroethane (100 mL) was shaken vigorously until it became homogeneous. With vigorous stirring, ammonium hydroxide (100 mL) and *p*-toluenesulfonyl chloride (4.45 g, 23.4 mmol) were added sequentially. The reaction was stirred overnight at room temperature. The product was present as a white precipitate, which was isolated by filtration to provide 1.97 g of *O*-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]hydroxylamine as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.0 (d, *J* = 8.2 Hz, 1H), 7.8 (d, *J* = 8.3 Hz, 1H), 7.5 (t, *J* = 7.1 Hz, 1H), 7.3 (t, *J* = 7.1 Hz, 1H), 5.6 (br s, 2H), 5.2 (br s, 2H), 4.5 (t, *J* = 7.8 Hz, 2H), 3.8 (t, *J* = 6.2 Hz, 2H), 2.9 (t, *J* = 7.6 Hz, 2H), 1.7-2.0 (m, 6H), 1.6 (m, 2H), 1.0 (t, *J* = 7.3 Hz, 3H); MS (APCI) *m/z* 328 $(M + H)^+$.

The filtrate with diluted with chloroform, washed with brine (3 x 100 mL), dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and concentrated under reduced pressure to provide 5.72 g additional product as a red semi-solid.

Part D

Acetone (444 mg, 7.65 mmol) was added to a solution of *O*-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]hydroxylamine (0.500 g, 1.53 mmol) in methanol (7 mL), and the reaction was stirred overnight at room temperature. The solvent was removed under reduced pressure and then further dried under high vacuum to provide 358 mg of propan-2-one *O*-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]oxime as a white solid, mp 115-117°C.

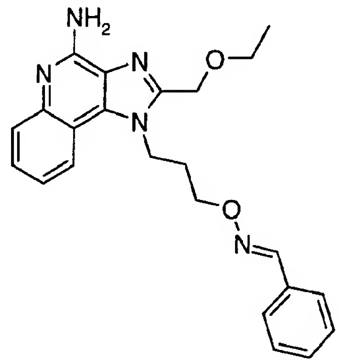
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.0 (d, *J* = 7.8 Hz, 1H), 7.7 (d, *J* = 8.3 Hz, 1H), 7.5 (t, *J* = 8.0 Hz, 1H), 7.3 (t, *J* = 8.1 Hz, 1H), 6.5 (br s, 2H), 4.5 (t, *J* = 7.2 Hz, 2H), 4.0 (t, *J* = 6.0 Hz, 2H), 2.9 (t, *J* = 7.5 Hz, 2H), 1.9-1.6 (m, 12H), 1.5 (m, 2H), 1.1 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (75 MHz, DMSO-d_6) δ 154.2, 153.4, 152.0, 144.8, 132.6, 128.4, 126.6, 126.4, 121.5, 120.3, 115.1, 71.9, 44.9, 30.0, 26.8, 26.5, 25.9, 22.3, 21.6, 15.4, 14.1;
MS (APCI) m/z 368 $(M + H)^+$;
HRMS (ESI) Theoretical mass: 368.2469, measured mass: 368.2450.

For Examples 5, 6, and 7 the final compounds were purified by flash chromatography using a 10 g silica gel cartridge (RediSep, ISCO, 230-400 mesh) attached to a gradient pump system, 254 nanometers (nm) UV detector, and fraction collector (ISCO CombiFlash Sg100c system). The column was equilibrated with dichloromethane:methanol with or without approximately 1% ammonium hydroxide, and the reaction mixture was injected onto the column. The mixture was eluted with a gradient program using a solvent system consisting of dichloromethane:methanol with or without approximately 1% ammonium hydroxide. The gradient started with a lower percentage of methanol (approximately 1%) and the percentage of methanol was gradually increased (to up to approximately 10%) to elute the desired compound. Fractions were examined by thin layer chromatography and by LC/MS and those containing the desired compound were combined and concentrated.

Example 5

Benzaldehyde *O*-[3-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime



Part A

Triphenylphosphine (8.71 g, 33.2 mmol) and *N*-hydroxyphthalimide (5.42 g, 33.2 mmol) were added to a solution of 2-ethoxymethyl-1-(3-hydroxypropyl)-1*H*-imidazo[4,5-*c*]quinoline (6.31 g, 22.1 mmol) in tetrahydrofuran (150 mL). The reaction was stirred under nitrogen and cooled to approximately 0°C. Diisopropyl azodicarboxylate (17.5 mL, 89.1 mmol) was then added dropwise over a period of 15 minutes. The solvent was removed under reduced pressure, and the residue was dissolved in chloroform (200 mL). The solution was extracted with 6 normal (N) hydrochloric acid (3 x 200 mL), and sodium hydroxide pellets were added to the combined extracts until the solution was basic. The aqueous solution was then extracted with chloroform (4 x), and the combined extracts were dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and concentrated under reduced pressure to provide 4 g of *O*-[3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]hydroxylamine.

Part B

Benzaldehyde (340 µL, 3.3 mmol) was added to a solution of *O*-[3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]hydroxylamine (1.00 g, 3.33 mmol) in methanol (4 mL), and the resulting solution was stirred overnight at room

temperature. The methanol was removed under reduced pressure to provide 1.42 g of benzaldehyde *O*-[3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime, which was used without purification.

Part C

The material from Part B was dissolved in dichloromethane (5 mL), and mCPBA (984 mg, 4.39 mmol) was added. The reaction was stirred for one hour and then diluted with dichloromethane. The solution was washed with saturated aqueous sodium bicarbonate (2 x 50 mL), dried over magnesium sulfate, filtered through a layer of CELITE filter aid, concentrated under reduced pressure, and further dried under high vacuum to provide 1.03 g of benzaldehyde *O*-[3-(2-ethoxymethyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime as a red, glassy solid.

Part D

Ammonium hydroxide (15 mL) was added with vigorous stirring to a solution of benzaldehyde *O*-[3-(2-ethoxymethyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime (1.03 g, 2.55 mmol) in dichloroethane (15 mL). *p*-Toluenesulfonyl chloride (572 milligrams (mg), 3.00 mmol) was added, and the reaction was stirred for two hours at room temperature. The reaction was diluted with dichloromethane, and the organic solution was washed with brine (2 x 50 mL), dried over magnesium sulfate, filtered through a layer of CELITE filter aid, concentrated under reduced pressure, and further dried under high vacuum to provide a brown and white solid. The solid was purified by flash chromatography using the method described above to provide 296 mg of benzaldehyde *O*-[3-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime as a brown powder, mp 133-135°C.

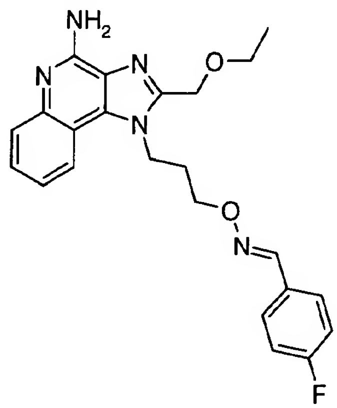
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.4 (s, 1H), 8.1 (d, *J* = 7.9 Hz, 1H), 7.7 (m, 3H), 7.5 (m, 4H), 7.2 (t, *J* = 7.1 Hz, 1H), 6.7 (br s, 2H), 4.8 (m, 4H), 4.4 (t, *J* = 5.6 Hz, 2H), 3.7 (q, *J* = 7.0 Hz, 2H), 2.3 (m, 2H), 1.2 (t, *J* = 6.8 Hz, 3H);

MS (APCI) *m/z* 404 (M + H)$^+$;

Anal. calcd for $C_{23}H_{25}N_5O_2$: C, 68.47; H, 6.25; N, 17.36. Found: C, 68.18; H, 6.08; N, 17.07.

Example 6

4-Fluorobenzaldehyde *O*-[3-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime



Part A

4-Fluorobenzaldehyde (357 µL, 3.37 mmol) was added to a solution of *O*-[3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]hydroxylamine (1.00 g, 3.33 mmol), prepared in Part A of Example 5, in methanol (4 mL), and the resulting solution was stirred overnight at room temperature. The methanol was removed under reduced pressure to provide 1.29 g of 4-fluorobenzaldehyde *O*-[3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime, which was used without purification.

Part B

The general method described in Part C of Example 5 was used to oxidize 4-fluorobenzaldehyde *O*-[3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime (1.29 g, 3.18 mmol) with mCPBA (855 mg, 3.81 mmol) to provide 851 mg of 4-fluorobenzaldehyde *O*-[3-(2-ethoxymethyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime as a red, tarry solid.

Part C

The general method described in Part D of Example 5 was used to aminate 4-fluorobenzaldehyde *O*-[3-(2-ethoxymethyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime (851 mg, 2.02 mmol). 4-Fluorobenzaldehyde *O*-[3-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime (346 mg) was obtained as a beige powder, mp 157-158°C.

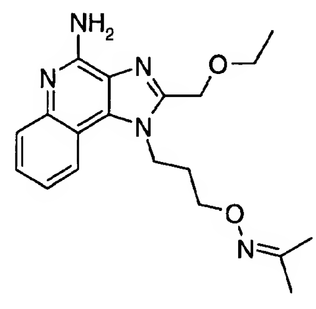
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.4 (s, 1H), 8.1 (d, J = 7.5 Hz, 1H), 7.7 (m, 2H), 7.6 (d, J = 8.4 Hz, 1H), 7.4 (t, J = 7.1 Hz, 1H), 7.3 (m, 2H), 7.1 (t, J = 8.2 Hz, 1H), 6.7 (br s, 2H), 4.8 (m, 4H), 4.3 (t, J = 5.6 Hz, 2H), 3.6 (q, J = 7.0 Hz, 2H), 2.3 (m, 2H), 1.2 (t, J = 7.0 Hz, 3H);

MS (APCI) *m/z* 422 (M + H)$^+$;

Anal. calcd for $C_{23}H_{24}FN_5O_2$: C, 65.54; H, 5.74; N, 16.62. Found: C, 65.32; H, 5.81; N, 16.46.

Example 7

Propan-2-one *O*-[3-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime



Part A

Acetone (193 mg, 3.33 mmol) was added to a solution of *O*-[3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]hydroxylamine (1.00 g, 3.33 mmol), prepared in Part A of Example 5, in methanol (4 mL), and the resulting solution was stirred overnight at room temperature. The methanol was removed

under reduced pressure to provide 1.06 g of propan-2-one *O*-[3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime, which was used without purification.

Part B

The general method described in Part C of Example 5 was used to oxidize propan-2-one *O*-[3-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime (1.06 g, 3.12 mmol) with mCPBA (838 mg, 3.74 mmol) to provide 729 mg of propan-2-one *O*-[3-(2-ethoxymethyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime as a red solid.

Part C

The general method described in Part D of Example 5 was used to aminate propan-2-one *O*-[3-(2-ethoxymethyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime (726 mg, 2.04 mmol). Propan-2-one *O*-[3-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime (136 mg) was obtained as an off-white crystalline solid, mp 109-111°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1 (d, *J* = 8.2 Hz, 1H), 7.8 (d, *J* = 8.4 Hz, 1H), 7.5 (t, *J* = 7.1 Hz, 1H), 7.3 (t, *J* = 7.1 Hz, 1H), 5.6 (br s, 2H), 4.8 (s, 2H), 4.75 (t, *J* = 6.1 Hz, 2H), 4.2 (t, *J* = 5.5 Hz, 2H), 3.6 (q, *J* = 7.0 Hz, 2H), 2.4 (m, 2H), 2.0 (s, 3H), 1.9 (s, 3H), 1.3 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 151.8, 149.5, 145.4, 134.5, 127.7, 127.5, 127.1, 122.7, 120.5, 115.8, 70.3, 66.6, 65.5, 44.1, 30.4, 22.3, 16.0, 15.5;

MS (APCI) *m/z* 356 $(M + H)^+$;

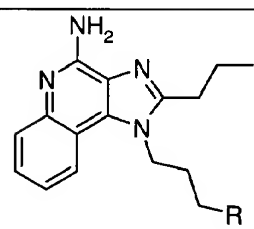
Anal. calcd for $C_{19}H_2\,N_5O_2$: C, 64.20; H, 7.09; N, 19.70. Found: C, 63.98; H, 7.22; N, 19.40.

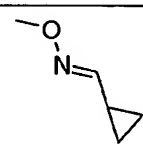
Examples 8-83

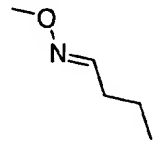
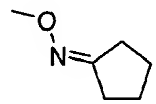
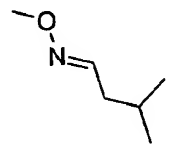
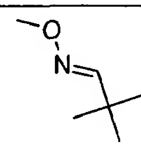
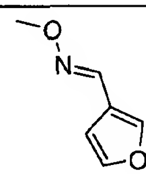
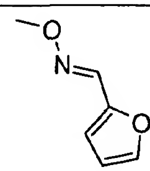
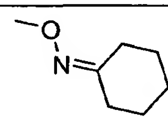
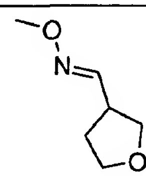
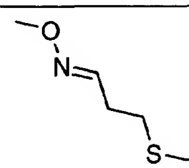
An aldehyde or ketone from the table below (1.1 equivalents, 0.071 mmol) was added to a test tube containing a solution of *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]hydroxylamine (20 mg, 0.066 mmol) in

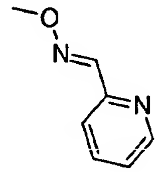
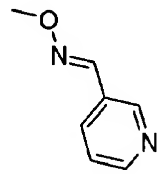
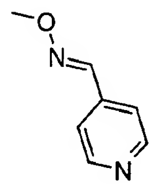
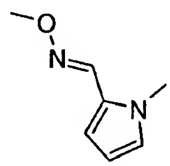
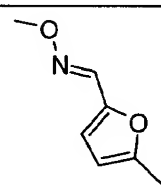
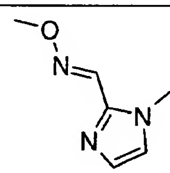
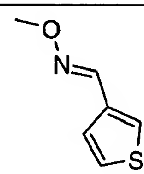
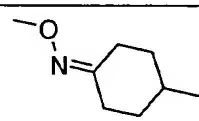
methanol (1 mL). The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). The solvent was removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters Fraction Lynx automated purification system. The prep HPLC fractions were analyzed using a Micromass LC-TOFMS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Column: Phenomenex Luna C18(2), 21.2 x 50 millimeters (mm), 10 micron particle size, 100 Angstroms (Å) pore; flow rate: 25 mL/min; non-linear gradient elution from 5-95% B in 9 min, then hold at 95% B for 2 min, where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile; fraction collection by mass-selective triggering. The table below shows the ketone or aldehyde used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

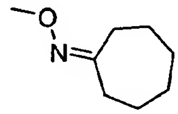
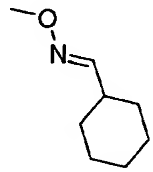
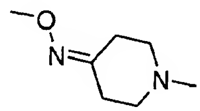
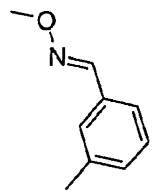
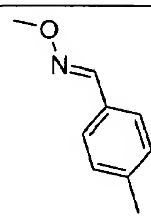
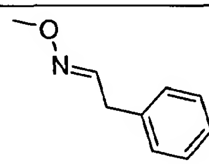
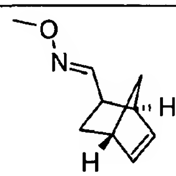
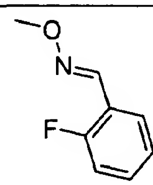
Examples 8-83

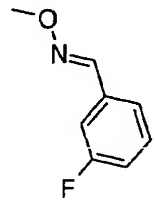
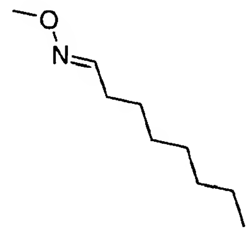
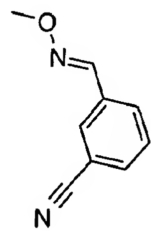
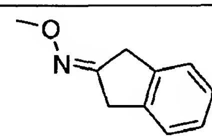
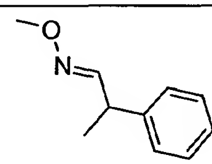
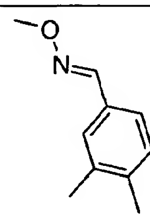
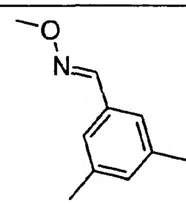


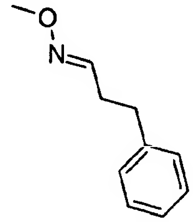
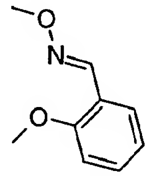
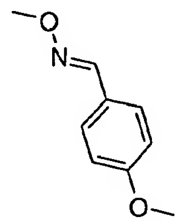
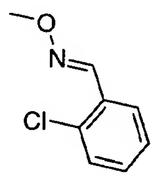
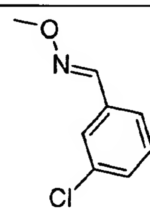
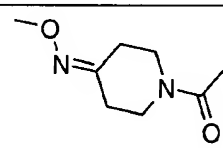
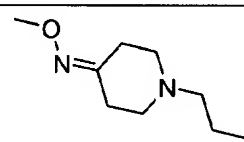
Ex.	Aldehyde or Ketone	R	Measured Mass (M+H)
8	Cyclopropane-carboxaldehyde		352.2163

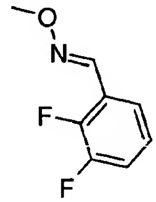
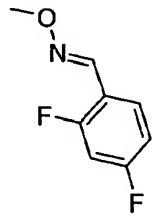
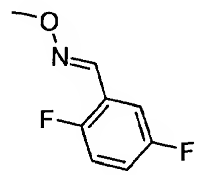
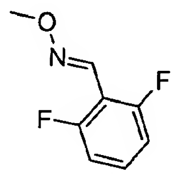
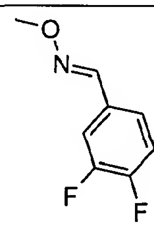
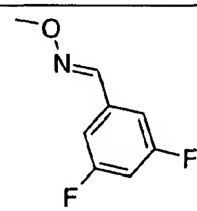
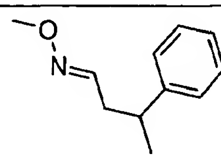
9	Butyraldehyde		354.2321
10	Cyclopentanone		366.2313
11	Isovaleraldehyde		368.2447
12	Trimethylacetaldehyde		368.2451
13	3-Furaldehyde		378.1914
14	Furfural		378.1929
15	Cyclohexanone		380.2452
16	Tetrahydrofuran-3-carboxaldehyde (50% in water)		382.2266
17	3-(Methylthio) propionaldehyde		386.2041

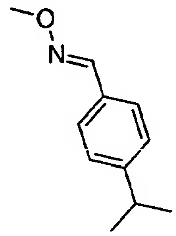
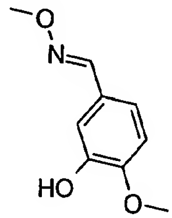
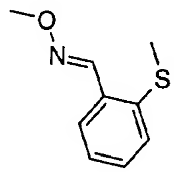
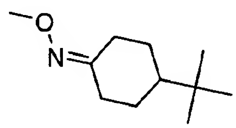
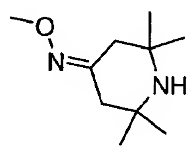
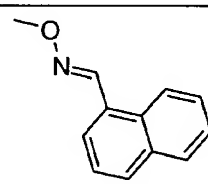
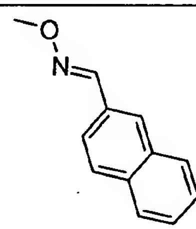
18	2-Pyridinecarboxaldehyde		389.2112
19	3-Pyridinecarboxaldehyde		389.2113
20	4-Pyridinecarboxaldehyde		389.2090
21	1-Methylpyrrole-2-carboxaldehyde		391.2253
22	5-Methylfurfural		392.2091
23	1-Methyl-2-imidazolecarboxaldehyde		392.2209
24	3-Thiophenecarboxaldehyde		394.1690
25	4-Methylcyclohexanone		394.2638

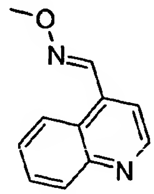
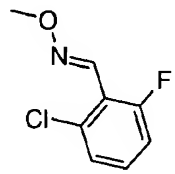
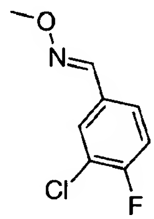
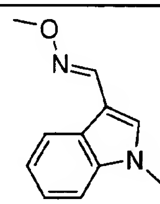
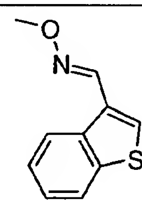
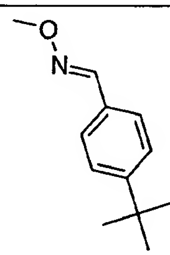
26	Cycloheptanone		394.2619
27	Cyclohexanecarboxaldehyde		394.2636
28	1-Methyl-4-piperidone		395.2582
29	*m*-Tolualdehyde		402.2304
30	*p*-Tolualdehyde		402.2317
31	Phenylacetaldehyde		402.2297
32	5-Norbornene-2-carboxaldehyde		404.2444
33	2-Fluorobenzaldehyde		406.2079

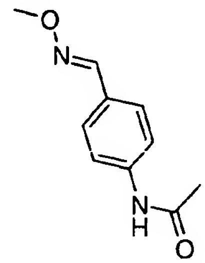
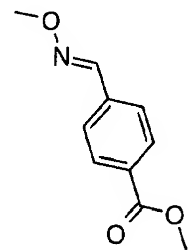
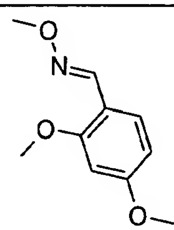
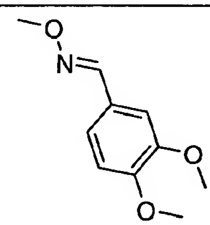
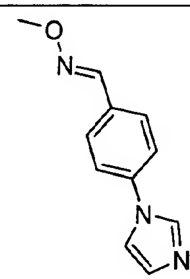
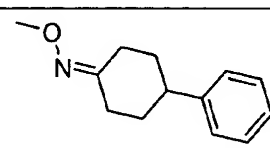
34	3-Fluorobenzaldehyde		406.2060
35	Octanal		410.2934
36	3-Cyanobenzaldehyde		413.2113
37	2-Indanone		414.2309
38	2-Phenylpropionaldehyde		416.2444
39	3,4-Dimethylbenzaldehyde		416.2476
40	3,5-Dimethylbenzaldehyde		416.2473

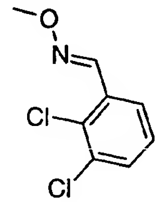
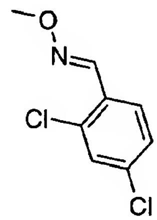
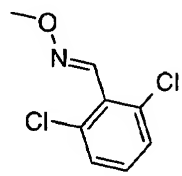
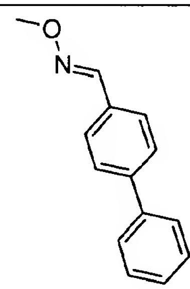
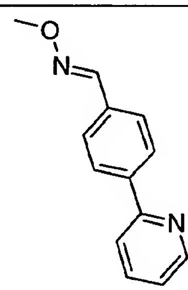
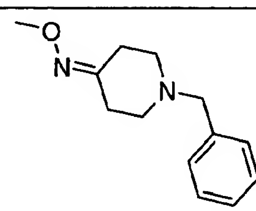
41	3-Phenylpropionaldehyde		416.2482
42	2-Methoxybenzaldehyde		418.2265
43	*p*-Anisaldehyde		418.2257
44	2-Chlorobenzaldehyde		422.1773
45	3-Chlorobenzaldehyde		422.1741
46	1-Acetyl-4-piperidone		423.2539
47	1-Propyl-4-piperidone		423.2877

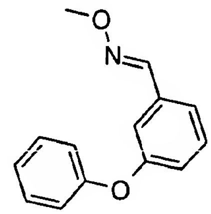
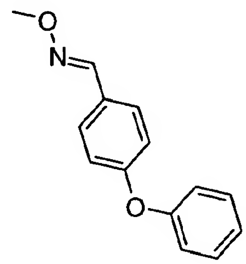
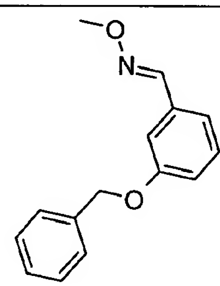
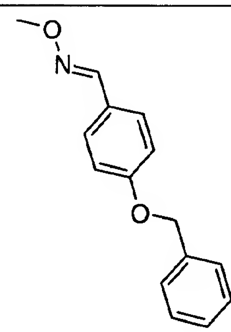
48	2,3-Difluorobenzaldehyde		424.1971
49	2,4-Difluorobenzaldehyde		424.1985
50	2,5-Difluorobenzaldehyde		424.1946
51	2,6-Difluorobenzaldehyde		424.1976
52	3,4-Difluorobenzaldehyde		424.1960
53	3,5-Difluorobenzaldehyde		424.1975
54	3-Phenylbutyraldehyde		430.2623

55	Cuminaldehyde		430.2630
56	3-Hydroxy-4-Methoxybenzaldehyde		434.2180
57	2-(Methylthio)benzaldehyde		434.2025
58	4-*tert*-Butylcyclohexanone		436.3089
59	2,2,6,6-Tetramethyl-4-piperidone		437.3042
60	1-Naphthaldehyde		438.2296
61	2-Naphthaldehyde		438.2321

62	4-Quinolinecarboxaldehyde		439.2276
63	2-Chloro-6-fluorobenzaldehyde		440.1650
64	3-Chloro-4-fluorobenzaldehyde		440.1657
65	1-Methylindole-3-carboxaldehyde		441.2405
66	Thianaphthene-3-carboxaldehyde		444.1878
67	4-*tert*-Butylbenzaldehyde		444.2747

68	4-Acetamidobenzaldehyde		445.2375
69	Methyl 4-formylbenzoate		446.2195
70	2,4-Dimethoxybenzaldehyde		448.2351
71	3,4-Dimethoxybenzaldehyde		448.2359
72	4-(1*H*-Imidazol-1-yl)benzaldehyde		454.2388
73	4-Phenylcyclohexanone		456.2742

74	2,3-Dichlorobenzaldehyde		456.1371
75	2,4-Dichlorobenzaldehyde		456.1389
76	2,6-Dichlorobenzaldehyde		456.1345
77	4-Biphenylcarboxaldehyde		464.2472
78	4-(2-Pyridyl)benzaldehyde		465.2433
79	1-Benzyl-4-piperidone		471.2900

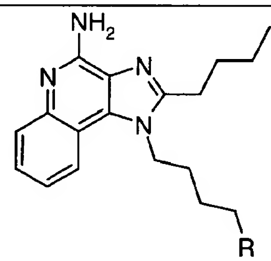
80	3-Phenoxybenzaldehyde		480.2427
81	4-Phenoxybenzaldehyde		480.2393
82	3-Benzyloxybenzaldehyde		494.2564
83	4-Benzyloxybenzaldehyde		494.2585

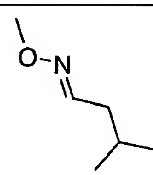
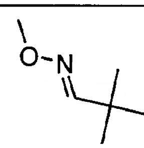
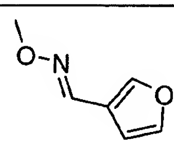
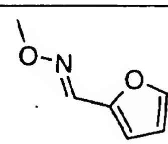
Examples 84-126

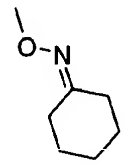
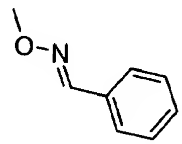
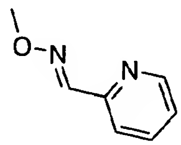
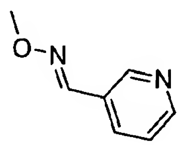
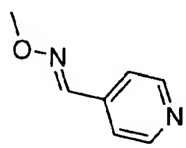
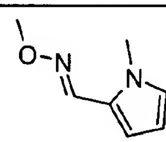
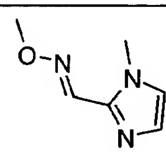
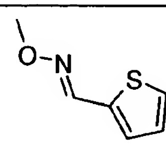
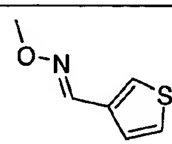
An aldehyde or ketone from the table below (1.1 equivalents, 0.11 mmol) was added to a test tube containing a solution of *O*-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]hydroxylamine (32 mg, 0.098 mmol) in methanol (1 mL). The test tube was capped and placed on a shaker at ambient temperature overnight (~18 hours). The solvent was removed by vacuum centrifugation. The

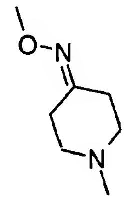
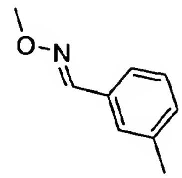
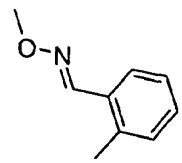
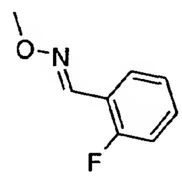
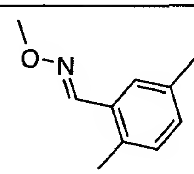
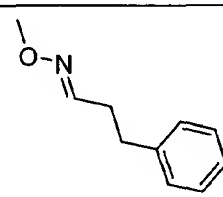
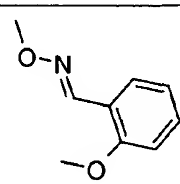
compounds were purified as described for Examples 8-83. The table below shows the ketone or aldehyde used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

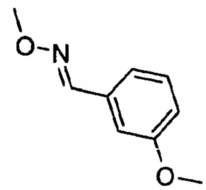
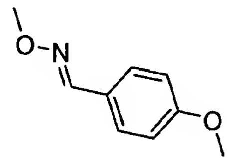
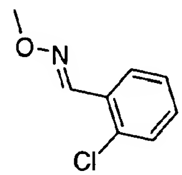
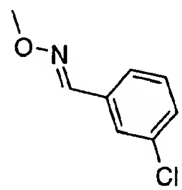
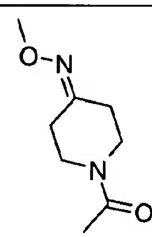
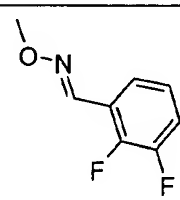
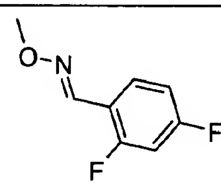
Examples 84-126

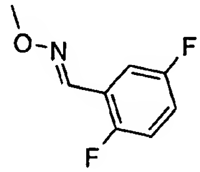
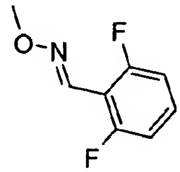
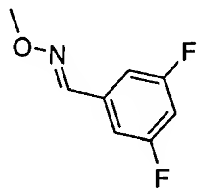
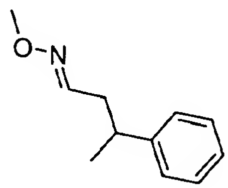
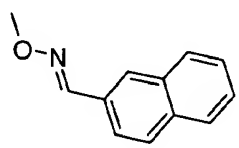
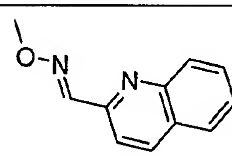
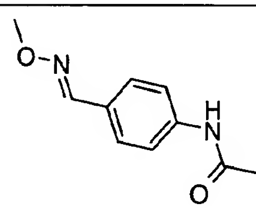


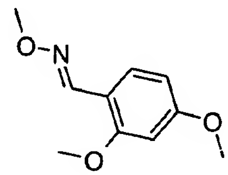
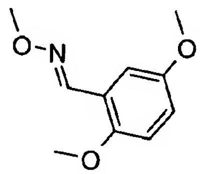
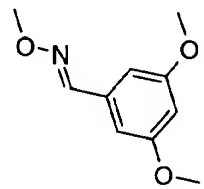
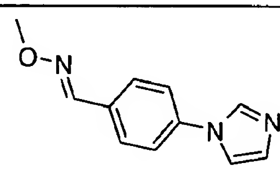
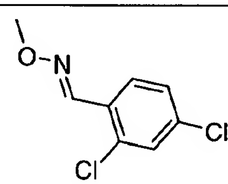
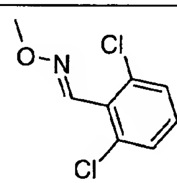
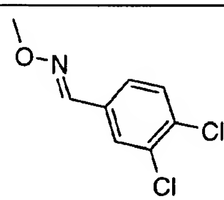
Ex.	Aldehyde or Ketone	R	Measured Mass (M+H)
84	Isovaleraldehyde		396.2747
85	Trimethylacetaldehyde		396.2743
86	3-Furaldehyde		406.2266
87	Furfural		406.2257

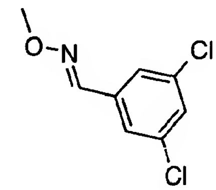
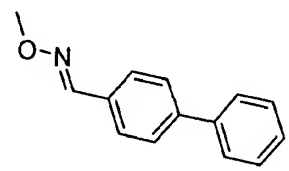
88	Cyclohexanone		408.2744
89	Benzaldehyde		416.2440
90	2-Pyridinecarboxaldehyde		417.2394
91	3-Pyridinecarboxaldehyde		417.2365
92	4-Pyridinecarboxaldehyde		417.2430
93	1-Methylpyrrole-2-carboxaldehyde		419.2578
94	1-Methyl-2-imidazolecarboxaldehyde		420.2485
95	2-Thiophenecarboxaldehyde		422.2002
96	3-Thiophenecarboxaldehyde		422.2031

97	1-Methyl-4-piperidone		423.2871
98	*m*-Tolualdehyde		430.2621
99	*o*-Tolualdehyde		430.2603
100	2-Fluorobenzaldehyde		434.2378
101	2,5-Dimethylbenzaldehyde		444.2778
102	3-Phenylpropionaldehyde		444.2782
103	2-Methoxybenzaldehyde		446.2560

104	3-Methoxybenzaldehyde		446.2574
105	*p*-Anisaldehyde		446.2578
106	2-Chlorobenzaldehyde		450.2086
107	3-Chlorobenzaldehyde		450.2083
108	1-Acetyl-4-piperidone		451.2798
109	2,3-Difluorobenzaldehyde		452.2256
110	2,4-Difluorobenzaldehyde		452.2295

111	2,5-Difluorobenzaldehyde		452.2298
112	2,6-Difluorobenzaldehyde		452.2282
113	3,5-Difluorobenzaldehyde		452.2297
114	3-Phenylbutyraldehyde		458.2908
115	2-Naphthaldehyde		466.2631
116	2-Quinolinecarboxaldehyde		467.2558
117	4-Acetamidobenzaldehyde		473.2665

118	2,4-Dimethoxybenzaldehyde		476.2665
119	2,5-Dimethoxybenzaldehyde		476.2667
120	3,5-Dimethoxybenzaldehyde		476.2677
121	4-(1*H*-Imidazol-1-yl)benzaldehyde		482.2682
122	2,4-Dichlorobenzaldehyde		484.1685
123	2,6-Dichlorobenzaldehyde		484.1673
124	3,4-Dichlorobenzaldehyde		484.1673

125	3,5-Dichlorobenzaldehyde		484.1679
126	4-Biphenylcarboxaldehyde		492.2738

CYTOKINE INDUCTION IN HUMAN CELLS

Compounds of the invention have been found to induce cytokine biosynthesis when tested using the method described below.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et. al. In “Cytokine Induction by the Immunomodulators Imiquimod and S-27609”, *Journal of Leukocyte Biology*, *58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank’s Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 micromolar (μM).

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (30-0.014 μM). The final concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at -30°C to -70°C until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

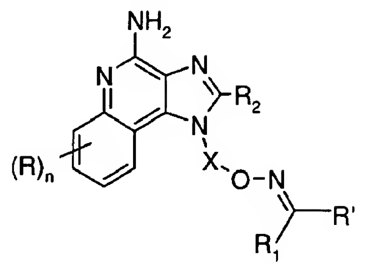
Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The

immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A compound of the formula (I):



I

wherein:

X is –CH(R_4)alkylene or –CH(R_4)alkenylene;

R_1 and R' are independently selected from the group consisting of

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-alkylene-aryl;

-heteroaryl;

-heterocyclyl; and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl or heterocyclyl substituted by one or more substituents selected from the group consisting of

-OH;

-alkyl;

-haloalkyl;

-hydroxyalkyl;

-O-alkyl;

-S-alkyl;

-O-haloalkyl;

-halogen;

-nitrile;

-aryl;

-heteroaryl;

-heterocyclyl;

-O-aryl;

-O-alkylene-aryl;

-C(O)-O-alkyl;

-C(O)-N(R_5)$_2$; and

-N(R_5)-C(O)-alkyl;

or R_1 and R' can join together to form a ring system containing one or two saturated or unsaturated rings optionally including one or more heteroatoms;

n is 0-4;

each R and R_2 are independently selected from the group consisting of hydrogen and non-interfering substituents;

R_4 is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups; and

each R_5 is independently selected from the group consisting of hydrogen, C_{1-10}alkyl, and C_{2-10}alkenyl;

or a pharmaceutically acceptable salt thereof.

2. The compound or salt of claim 1 which induces the synthesis of at least one cytokine.

3. The compound or salt of claim 1 wherein X is CH(R_4)C_{1-5}alkylene.

4. The compound or salt of claim 3 wherein X is propylene or butylene.

5. The compound or salt of claim 1 wherein R_1 is selected from the group consisting of -aryl, -heteroaryl, and -alkyl, wherein the -aryl, -heteroaryl, and -alkyl are optionally substituted.

6. The compound or salt of claim 1 wherein R' is hydrogen.

7. The compound or salt of claim 5 wherein R_1 is aryl or substituted aryl and R' is hydrogen.

8. The compound or salt of claim 5 wherein R_1 is heteroaryl or substituted heteroaryl and R' is hydrogen.

9. The compound or salt of claim 1 wherein R_1 and R' join together to form a ring system.

10. The compound or salt of claim 9 wherein the ring system is optionally substituted by one or more substituents selected from the group consisting of -alkyl, -aryl, -alkylene-aryl, and -C(O)-alkyl.

11. The compound or salt of claim 1 wherein each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl.

12. The compound or salt of claim 1 wherein R_2 is selected from the group consisting of:

-hydrogen;
-alkyl;
-alkenyl;
-aryl;
-heteroaryl;
-heterocyclyl;
-alkylene-Y-alkyl;
-alkylene-Y- alkenyl;
-alkylene-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_5)_2$;

-C(O)-C_{1-10}alkyl;

-C(O)-O-C_{1-10}alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-C(O)-aryl; and

-C(O)-heteroaryl;

wherein:

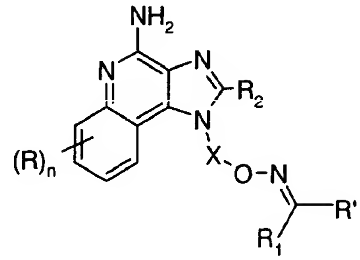
Y is –O– or –$S(O)_{0-2}$-; and

each R_5 is independently selected from the group consisting of hydrogen, C_{1-10}alkyl, and C_{2-10}alkenyl.

13. The compound or salt of claim 12 wherein R_2 is selected from the group consisting of hydrogen, alkyl, and alkylene-O-alkyl.

14. The compound or salt of claim 1 wherein n is 0.

15. A compound of the formula (I):



I

wherein:

X is $-CH(R_4)$alkylene or $-CH(R_4)$alkenylene;

R_1 and R' are independently selected from the group consisting of

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-alkylene-aryl;

-heteroaryl;

-heterocyclyl; and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl or heterocyclyl substituted by one or more substituents selected from the group consisting of

-OH;

-alkyl;

-haloalkyl;

-hydroxyalkyl;

-O-alkyl;

-S-alkyl;

-O-haloalkyl;

-halogen;

-nitrile;

-aryl;

-heteroaryl;

-heterocyclyl;

-O-aryl;

-O-alkylene-aryl;

-C(O)-O-alkyl;

-C(O)-N(R_5)$_2$; and

-N(R_5)-C(O)-alkyl;

or R_1 and R' can join together to form a ring system containing one or two saturated or unsaturated rings optionally including one or more heteroatoms;

n is 0-4;

each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkylene-Y-alkyl;

-alkylene-Y- alkenyl;

-alkylene-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-N(R_5)$_2$;

-C(O)-C_{1-10}alkyl;

-C(O)-O-C_{1-10}alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-C(O)-aryl; and

-C(O)-heteroaryl;

wherein:

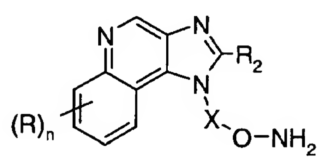
Y is –O– or $-S(O)_{0-2}-$;

R_4 is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups; and

each R_5 is independently selected from the group consisting of hydrogen, C_{1-10}alkyl, and C_{2-10}alkenyl;

or a pharmaceutically acceptable salt thereof.

16. A compound of the formula (XIV):



XIV

wherein:

X is $-CH(R_4)$alkylene or $-CH(R_4)$alkenylene;

n is 0-4;

each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkylene-Y-alkyl;

-alkylene-Y- alkenyl;

-alkylene-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

$-N(R_5)_2$;

$-C(O)-C_{1-10}$alkyl;

$-C(O)-O-C_{1-10}$alkyl;

$-N_3$;

-aryl;

-heteroaryl;

-heterocyclyl;

-C(O)-aryl; and

-C(O)-heteroaryl;

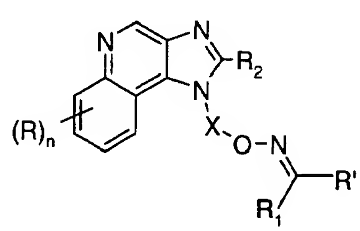
wherein:

Y is –O– or $-S(O)_{0-2}$-; and

each R_5 is independently selected from the group consisting of hydrogen, C_{1-10}alkyl, and C_{2-10}alkenyl; and

R_4 is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups.

17. A compound of the formula (XV):



XV

wherein:

X is $-CH(R_4)$alkylene or $-CH(R_4)$alkenylene;

R_1 and R' are independently selected from the group consisting of

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-alkylene-aryl;

-heteroaryl;

-heterocyclyl; and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl or heterocyclyl substituted by one or more substituents selected from the group consisting of

-OH;

-alkyl;

-haloalkyl;

-hydroxyalkyl;

-O-alkyl;

-S-alkyl;

-O-haloalkyl;

-halogen;

-nitrile;

-aryl;

-heteroaryl;

-heterocyclyl;

-O-aryl;

-O-alkylene-aryl;

-C(O)-O-alkyl;

-C(O)-$N(R_5)_2$; and

-$N(R_5)$-C(O)-alkyl;

or R_1 and R' can join together to form a ring system containing one or two saturated or unsaturated rings optionally including one or more heteroatoms;

n is 0-4;

each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkylene-Y-alkyl;

-alkylene-Y- alkenyl;

-alkylene-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_5)_2$;

-C(O)-C_{1-10}alkyl;

-C(O)-O-C_{1-10}alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-C(O)-aryl; and

-C(O)-heteroaryl;

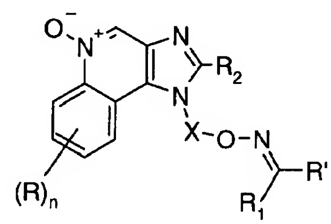
wherein:

Y is –O– or $-S(O)_{0-2}-$;

R_4 is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups; and

each R_5 is independently selected from the group consisting of hydrogen, C_{1-10}alkyl, and C_{2-10}alkenyl.

18. A compound of the formula (XVI):



XVI

wherein:

X is $-CH(R_4)$alkylene or $-CH(R_4)$alkenylene;

R_1 and R' are independently selected from the group consisting of

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-alkylene-aryl;

-heteroaryl;

-heterocyclyl; and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl or heterocyclyl substituted by one or more substituents selected from the group consisting of

-OH;

-alkyl;

-haloalkyl;

-hydroxyalkyl;

-O-alkyl;

-S-alkyl;

-O-haloalkyl;

-halogen;

-nitrile;

-aryl;

-heteroaryl;

-heterocyclyl;

-O-aryl;

-O-alkylene-aryl;

-C(O)-O-alkyl;

-C(O)-N(R_5)$_2$; and

-N(R_5)-C(O)-alkyl;

or R_1 and R' can join together to form a ring system containing one or two saturated or unsaturated rings optionally including one or more heteroatoms;

n is 0-4;

each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and trifluoromethyl;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkylene-Y-alkyl;

-alkylene-Y- alkenyl;

-alkylene-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_5)_2$;

-$C(O)$-C_{1-10}alkyl;

-$C(O)$-O-C_{1-10}alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-C(O)-aryl; and

-C(O)-heteroaryl;

wherein:

Y is –O– or –$S(O)_{0-2}$-;

R_4 is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups; and

each R_5 is independently selected from the group consisting of hydrogen, C_{1-10}alkyl, and C_{2-10}alkenyl.

19. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

20. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 15 in combination with a pharmaceutically acceptable carrier.

21. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound of claim 1 to the animal.

22. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound of claim 15 to the animal.

23. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound of claim 1 to the animal.

24. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound of claim 15 to the animal.

25. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound of claim 1 to the animal.

26. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound of claim 15 to the animal.

OXIME SUBSTITUTED IMIDAZOQUINOLINES

ABSTRACT OF THE DISCLOSURE

Imidazoquinoline compounds with an oxime substituent at the 1-position, pharmaceutical compositions containing the compounds, intermediates, and methods of use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.